

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

REC'D 30 MAR 2004

WIPO PCT

Applicant's or agent's file reference 4-32456A/USN	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/EP 03/03864	International filing date (day/month/year) 14.04.2003	Priority date (day/month/year) 15.04.2002
International Patent Classification (IPC) or both national classification and IPC C07C233/63		
Applicant NOVARTIS AG		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 1 sheets.

3. This report contains indications relating to the following items:

I ☒ Basis of the opinion

II ☐ Priority

III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability



IV ☐ Lack of unity of invention

V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

VI ☐ Certain documents cited

VII ☐ Certain defects in the international application

VIII ☐ Certain observations on the international application

Date of submission of the demand 06.11.2003	Date of completion of this report 29.03.2004
Name and mailing address of the International preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Slootweg, A Telephone No. +49 89 2399-8326 <div style="text-align: right;">  </div>

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. **PCT/EP 03/03864**

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*):

Description, Pages

1-5 as originally filed

Claims, Numbers

1-9 received on 16.02.2004 with letter of 16.02.2004

Drawings, Sheets

1/1 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. **PCT/EP 03/03864**

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 2

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. see separate sheet are so unclear that no meaningful opinion could be formed (*specify*):

see separate sheet

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the Standard.

☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1,3-9
	No: Claims	
Inventive step (IS)	Yes: Claims	6-9
	No: Claims	1,3-5
Industrial applicability (IA)	Yes: Claims	1-9
	No: Claims	

2. Citations and explanations

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP 03/03864

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. Claim 2 defines a process for preparing crystals of nateglinide as defined in claim 1 by a) dissolving in a first solvent at an ambient temperature to dissolve the nateglinide, then b) treating the solution with a second solvent in which nateglinide is only poorly soluble to induce crystallization, and c) isolating and drying the crystals formed.
2. The process of claim 2 defines "an ambient temperature". The skilled man would consider the term "ambient temperature" to be equivalent to a temperature range ranging around room temperature (around 20°C plus or minus 20°C at most). From claim 4, however, it is clear that the expression includes room temperature to the boiling point of the solvent. These two definitions in claim 2 and 4 are considered to be contradictory. The expression "an ambient temperature" in claim 2 cannot, therefore, be considered to be clear (Art. 6 PCT), the expression used in claim 4 can, however, be considered to be clear.
3. In the document D1 (D1 = US-A-5 463 116) examples are disclosed in which nateglinide is first dissolved in one solvent in which it is readily soluble, and then treated with another solvent in which nateglinide is more sparingly soluble to induce precipitation of nateglinide and the subsequent isolation and drying of the crystals (see the description in col. 4, l. 54-60 and for example, example A1 in col. 7). This example falls under the process definition given in claim 2.
The process according to D1, does not, however, yield the crystal product as defined in present claim 1. It appears, therefore, that not all the essential features which are necessary to achieve the desired product have been defined in claim 2. Claim 2, therefore, represents a problem to be solved by the skilled man, namely to find the relevant first and second solvents and conditions, such as choice of temperature, by which the desired product can be obtained. Claim 2 cannot, therefore, be considered to satisfy Art. 6 PCT.
4. Due to this lack of clarity and disclosure it is not at present possible to examine claim 2 for novelty and inventive step.

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

5. The chemical name of nateglinide should be included in the claims for reasons of clarity (Art. 6 PCT).
6. Claim 1 defines "A crystal form of nateglinide having a melting point **about** 108°C". The term "about" is inherently unclear and renders the feature to which it refers also unclear (Art. 6 PCT). For the interpretation of the meaning of the expression "about 108°C" reference has been made to the description. From the description it appears that the melting point was determined by the DSC method (see the description on p. 2, l. 21-22), which method has an apparent error of around 2°C (see the description p. 2, l. 19-20). The temperature definition "**about** 108°C" can therefore be interpreted by the skilled man to indicate a temperature in the range of "106 to 110°C".
7. The document D1 (D1 = US-A-5 463 116) describes different polymorphic crystals of nateglinide [N-(trans-4-isopropylcyclohexylcarbonyl)-D-Phenylalanine] having a melting point of 138 to 141°C (the H-type) and crystals having a melting point of 128 to 131°C (the B-type).
8. The document D2 (G. LI ET AL, 'YAOXUE XUEBAO', 36/7/00-00-2001, 532-534) discloses crystals of nateglinide having a melting point of 172,04 degree (the S-form).
9. The melting points of the crystals disclosed in D1 and D2 are such that the crystals having a melting point as defined in claim 1 of "**about** 108°C" can be considered not be disclosed in the prior art. The subject-matter of claim 1 can, therefore, be considered to satisfy the requirements of Art. 33 (2) PCT.
10. The problem to be solved with respect to the documents cited in the search report can be considered to be, to provide further crystal forms of nateglinide.
11. The preparation of polymorphs of nateglinide is considered to be a priori obvious from D1 and D2 (Art. 33 (3) PCT).
12. The solution presented in claim 1 is the provision of the novel crystal form of nateglinide having a melting point of **about** 108°C. Apart from the obviously different

melting point of the new polymorph no further advantages or surprising properties have been shown. The crystals of nateglinide as defined in claim 1 are, therefore, considered to be obvious alternatives to the crystal forms known from D1 and D2. It is therefore considered that the subject-matter of claim 1 does not satisfy the requirements of Art. 33 (3) PCT.

13. The process features described in claims 3-5 have been used in the examples of D1 for the same purpose. These claims cannot therefore be considered to satisfy Art. 33 (3) PCT.
14. The feature described in claim 6, the first solvent being a mixture of ethanol and toluene, is not known from the prior art (Art. 33 (2) PCT). It is credible that this selection of solvents is responsible for yielding the crystals having a melting point of "about 108°C". That such a choice of solvents would yield crystals having a melting point of "about 108°C" could not have been predicted from the prior art. Claim 6 can, therefore, be considered to satisfy Art. 33 (3) PCT.
15. Claims 7-9 are dependent on claim 6 and can, therefore, also be considered to satisfy Art. 33 (2) and (3) PCT.

REPLACED BY
ART. 34 AMDTWhat is claimed is:

1. A crystal form of nateglinide having a melting point of about 108°C; or solvates thereof.
2. A method for the production of R'-type crystal form of nateglinide wherein the method comprises;
 - (a) dissolving nateglinide in any of its forms in a first solvent in which nateglinide is readily soluble at an ambient temperature to form a solution;
 - (b) treating the solution with a second solvent which is miscible with the first solvent, and in which nateglinide is only poorly soluble to induce precipitation of R'-type crystals of nateglinide; and
 - (c) isolating and drying the precipitated crystal form of nateglinide.
3. The method of claim 2, wherein the precipitation of the crystal form of nateglinide is induced by stirring, cooling or by adding seed crystals of nateglinide.
4. The method of claim 2, wherein the ambient temperature ranges from room temperature to the boiling point of the solvent.
5. The method of claim 2, wherein the crystal form of nateglinide is dried under atmospheric or reduced pressure at a temperature ranging from room temperature to 70°C.
6. The method of claim 2, wherein the first solvent is a mixture of ethanol and toluene;
7. The method of claim 6, wherein the second solvent is water containing hydroxypropylmethylcellulose.
8. The method of claim 7, wherein the first solvent contains 50% of ethanol by volume; the second solvent contains 1% of hydroxypropylmethylcellulose; and the ratio of the first solvent to the second solvent is 1 to 7 by volume.
9. The method of claim 8, wherein the ambient temperature is room temperature; and the crystal form of nateglinide is dried under reduced pressure at a temperature ranging from room temperature to 50°C.